



Skin Cancer Risk in Relation to Toenail Arsenic Concentrations in a US Population-based Case-Control Study

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Arsenic is a known carcinogen specifically linked to skin cancer occurrence in regions with highly contaminated drinking water or in individuals who took arsenic-containing medicines. Presently, it is unknown whether such effects occur at environmental levels found in the United States. To address this question, the authors used data collected on 587 basal cell and 284 squamous cell skin cancer cases and 524 controls interviewed as part of a case-control study conducted in New Hampshire between 1993 and 1996. Arsenic was determined in toenail clippings using instrumental neutron activation analysis. The odds ratios for squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) were close to unity in all but the highest category. Among individuals with toenail arsenic concentrations above the 97th percentile, the adjusted odds ratios were 2.07 (95% confidence interval (CI): 0.92, 4.66) for SCC and 1.44 (95% CI: 0.74, 2.81) for BCC, compared with those with concentrations at or below the median. While the risks of SCC and BCC did not appear elevated at the toenail arsenic concentrations detected in most study subjects, the authors cannot exclude the possibility of a dose-related increase at the highest levels of exposure experienced in the New Hampshire population. *Am J Epidemiol* 2001;153:559–65.

arsenic; case-control studies; metals, heavy; neoplasms, basal cell; neoplasms, squamous cell; skin neoplasms; water

Arsenic, a ubiquitous metalloid element, is a known human carcinogen and is specifically linked to skin cancer occurrence at high levels of exposure (1, 2). Epidemiologic data regarding drinking water arsenic and skin cancer have come largely from a region in the southwest of Taiwan that had well water arsenic concentrations as high as 1,220 µg/liter (3). In a household survey, skin cancer prevalence was about eight times higher in villages with a median drinking water concentration of 800 µg/liter compared with those with a median concentration of 170 µg/liter (3). In the United States, the maximum contaminant level for arsenic in public drinking water permitted by the Environmental Protection Agency was 50 µg/liter. This level is several times lower than the reference category in the Taiwanese study. Risk assessment models have relied on low-dose

extrapolation of the Taiwanese data, and later analyses indicate an excess cancer risk below the current maximal contaminant level (4). In the absence of direct data, the shape of the dose-response curve at the lower end of the exposure range remains speculative. Yet, because of accumulating data on the health effects of arsenic, the US Environmental Protection Agency recently reduced the maximal contaminant level to 10 µg/liter, half a magnitude lower than the previous standard (5).

Prior epidemiologic studies in the United States have found no relation between skin cancer and drinking water arsenic concentrations (6–9); however, these studies involved ecologic analyses using geographic areas with widely varying arsenic levels or included too few subjects to detect small elevations in risk. Studies based on skin cancer mortality (10) were possibly inconclusive because non-melanoma skin cancer is rarely fatal. Arsenic concentrations in toenails, which presumably reflect body burden from all sources of exposure, correlate with arsenic concentrations found in drinking water in areas with high arsenic levels (11, 12). In areas with low water levels of arsenic, however, other sources of exposure (i.e., food or occupation) may be more important (12); thus, in such areas, substantial misclassification could result from an exposure measure based on water concentrations alone. As part of a US population-based case-control study of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) of the skin, an assessment was made of the risks of these malignancies in relation to arsenic concentrations measured in individual toenail clipping samples.

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Abbreviations: BCC, basal cell carcinoma; CI, confidence interval; SCC, squamous cell carcinoma; SE, standard error.

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MATERIALS AND METHODS

Study group

A detailed account of the study design appears elsewhere (13). Briefly, we enlisted the collaboration of dermatologists and pathology laboratories throughout New Hampshire and bordering regions to identify cases of BCC and SCC (14). We selected for interview a sample of BCC and all cases of invasive SCCs diagnosed among New Hampshire residents, aged 25–74 years, from July 1, 1993, to June 30, 1995, identified through our survey by March 1996. In this age group and diagnostic period, there was an almost 4/1 BCC/SCC ratio. For efficiency, we chose a 2/1 BCC/SCC ratio of cases and randomly sampled according to the age and sex distribution of the total identified cases of BCCs to ensure that the subset would be representative of the population of BCC cases at large. To be eligible for the study, subjects were required to have a listed telephone number and to speak English. We sought physician consent before contacting eligible BCC and SCC patients. Of the 882 BCC and 471 SCC cases initially selected, 16 percent lacked a listed telephone number. All cases we contacted spoke English. Of the 1,143 potential participants, less than 1 percent ($n = 1$) of the physicians denied patient contact; 3 percent ($n = 31$) were reported as deceased by a household member or physician; and, in 1 percent ($n = 10$) of the households, no one answered after 40 attempts distributed over days, evenings, and weekends, 16 percent ($n = 178$) declined participation, and 2 percent ($n = 27$) were mentally incompetent or too ill to take part. We interviewed a total of 603 BCC and 293 SCC cases. For the present study, we included the 587 (97.3 percent) BCC and 284 (96.9 percent) SCC cases from whom we obtained and analyzed a toenail clipping sample for arsenic.

We chose a control group from among New Hampshire residents aged 25–74 years, frequency matched on age (25–34, 35–44, 45–54, 55–64, 65–69, 70–74 years) and sex to the combined distribution of the SCC and BCC cases. To select controls for cases aged less than 65 years, we used population lists obtained annually from the New Hampshire Department of Transportation. The file contains the names and addresses of those holding a valid driver's license for the state of New Hampshire. We selected controls for cases aged 65 years and older from data files provided annually by the Health Care Financing Administration's Medicare Program. The method of control selection in our study has been successfully used in other case-control studies conducted in the region (15).

We attempted to obtain an equal number of controls to BCC cases (or a 2/1 ratio to SCC cases). For interviewing purposes, controls were randomly assigned a comparable reference date to the cases' diagnosis dates. Of the 1,051 controls selected, 21 percent ($n = 224$) did not have an identifiable telephone number, and 1 percent ($n = 7$) were non-English speaking. Of the 820 potential participants, 2 percent ($n = 12$) were reported as deceased by a member of the household; in 2 percent ($n = 12$) of the households, no one answered after 40 attempts distributed over days, evenings, and weekends; 228 (28 percent) declined; and 28 (3 percent)

were mentally incompetent or too ill to take part. A total of 540 controls were interviewed, of which 524 (97.0 percent) had a toenail sample analyzable for arsenic.

Personal interview

Beginning in January 1994, we sent an introductory letter to potential cases and controls explaining the general purpose of the study and that an interviewer would soon telephone. Those who agreed to take part underwent a detailed in-person interview, usually at their home. Questions covered sociodemographic information (including level of education), use of tobacco, and medical history (including previous radiotherapy) prior to the reference date. Participants were queried about their skin sensitivity to the sun after first exposure in the summer and after prolonged exposure (i.e., tendency to sunburn).

Questions relating to household water supply included type of water source used in their current residence (e.g., private well vs. public water), years of use of their current water system, and use of water filters. For private, domestic systems, we asked whether the water source was a dug/surficial well, spring, or deep/artesian well. We further asked the average number of glasses of water they consumed each day from the household water system. In 1995, we began collecting a tap water sample from participants' homes to permit comparison of arsenic concentrations in water with those in toenails (12). The case-control status and main objectives of the study were not disclosed to the interviewers. To ensure consistent quality of the study interviewer, interviews were tape recorded with the consent of the participants and routinely monitored by the interviewer supervisor (<1 percent of participants refused to be taped). To assess comparability of cases and controls, we asked subjects if they currently held a driver's license or a Medicare enrollment card.

Arsenic determinations

In addition to the study interview, we requested a toenail clipping sample for analysis of arsenic. Subjects were mailed the instructions and materials to save a toenail clipping specimen prior to the interview; a self-addressed envelope was left for those who needed to send their sample in after the interview. Samples were analyzed for arsenic using instrumental neutron activation analysis at the University of Missouri's research reactor center (Columbia, Missouri) (16). Prior to analysis, nail samples were carefully washed to remove external contamination. Each batch of analyses included quality control samples composed of matrix-matched samples with known content and analytical blanks along with study samples and standards. The between-assay coefficient of variability for matrix-matched samples is about 8 percent. All samples were labeled with an identification number that did not reveal the case-control status of the study participants.

Statistical analysis

We classified cases (i.e., BCC, SCC) based on their first primary skin cancer diagnosed during our survey. Controls

selected for interview who had skin cancer before the study period (or who subsequently developed skin cancer) remained as controls in the primary analysis. Likewise, a case of SCC was analyzed as such, even if he or she later developed BCC or had a BCC before our survey period. Nonmelanoma skin cancer is highly curable. Therefore, it is usually possible to distinguish new primaries from recurrences. Classification of subjects according to this plan should result in relative risk estimates that are accurate estimates of incidence density ratios (17).

To assess the relation between toenail arsenic and the risk of BCC and SCC, we first conducted a logistic regression analysis using categories of toenail arsenic, classifying subjects by percentiles of the control distribution. To evaluate the form of the dose-response function, we plotted the smoothed observed proportions of cases as a function of log toenail arsenic values (18). Since the distribution of toenail arsenic values was right skewed, a natural log transformation was used to provide more normally distributed data. We used logistic regression to model the continuous arsenic values using both linear and quadratic models (19). Separate logistic regression models were run for each histologic type of skin cancer, BCC and SCC. All models controlled for age and sex. We conducted the analyses controlling for the original age categories applied for control selection and compared the results using age as a continuous variable. Because results were essentially the same, we used continuous age in the final models. We further evaluated the potentially confounding effects of educational attainment (high school or less, college, or graduate school), smoking status (never, former, or current), skin reaction to first exposure to the sun in the summer (blister, peel, mildly burn, or tan) or after prolonged exposure (very tan, moderately tan, mildly tan, or freckle/no tan), and history of radiotherapy (no or yes).

RESULTS

Selected characteristics of cases and controls are shown in table 1. BCC cases tended to be younger than SCC cases (table 1). Controls were comparable with the combined age and sex distribution of the BCC and SCC cases because of matching (table 1). Nearly all subjects reported being of the White race, especially the BCC and SCC cases (table 1). The level of educational attainment was somewhat lower among controls than cases, whereas the history of cigarette smoking was slightly higher (table 1). Compared with controls, a smaller percentage of both BCC and SCC cases tended to tan with first summer or prolonged sun exposure, and a higher percentage had a history of radiotherapy (table 1). Overall, 38 percent of the study participants reported current use of a private water supply at their home (table 1). About 30 percent currently had a drilled or bedrock well, and about 8 percent had a shallow or dug well or spring. On average, participants used their current water system for over 15 years.

The toenail arsenic concentration ranged from 0.01 to 0.81 $\mu\text{g/g}$ among controls, from 0.01 to 2.03 $\mu\text{g/g}$ among BCC cases, and from 0.01 to 2.57 $\mu\text{g/g}$ among SCC cases. The geometric mean values of toenail arsenic were 0.098

$\mu\text{g/g}$ (standard error (SE) of the geometric mean = 0.003), 0.090 $\mu\text{g/g}$ (SE = 0.004), and 0.094 $\mu\text{g/g}$ (SE = 0.003) among BCC and SCC cases and controls, respectively. In the categorical data analysis, the odds ratios for SCC and BCC were close to unity in all but the highest category (table 2). Among those with toenail arsenic concentrations above the 97th percentile, the odds ratio for SCC was 2.07 (95 percent confidence interval (CI): 0.92, 4.66), and for BCC it was 1.44 (95 percent CI: 0.74, 2.81) (table 2). With the linear model, the odds ratio per $\mu\text{g/g}$ increase was 1.08 (95 percent CI: 0.85, 1.36) for SCC and 1.03 (95 percent CI: 0.85, 1.25) for BCC. By inspection, the quadratic model appeared to fit the observed data. However, the addition of the quadratic term to the linear model was not statistically significant for BCC ($p = 0.34$) or SCC after excluding the case with the highest arsenic concentration ($p = 0.043$ overall; $p = 0.13$ for the model excluding a value above 2 $\mu\text{g/g}$). Adjustment for other covariates had no appreciable effect on the relative risk estimates.

DISCUSSION

In our case-control study of skin cancer conducted among New Hampshire residents, toenail arsenic concentrations were unrelated to risk at levels most commonly encountered in the population we studied. However, for SCC, we found some evidence of an increased risk at the highest levels of exposure, but with wide confidence intervals. For BCC, the relative risk estimates were closer to unity.

Despite concerns regarding the potential carcinogenic effects of low levels of arsenic exposure, relatively few studies have examined this issue in the United States. Earlier US studies of water arsenic and skin cancer were, for the most part, ecologic studies using broad geographic areas with varying arsenic concentrations. Thus, there was likely significant misclassification of individuals who drank arsenic-containing water. Additionally, one of the US studies (10) used mortality rates, a poor measure of non-melanoma skin cancer occurrence. Studies conducted in regions with unusually elevated well water concentrations of arsenic in Alaska ($n = 59$ households) (8) and California ($n = 76$ households) (9) were not designed to look at long-term effects such as cancer and had too few subjects to detect an excess skin cancer risk.

The skin cancer prevalence study reported by Tseng et al. (3) involved over 40,000 households from the southwest coast of Taiwan (primarily Chai-yi and Tainan counties). A striking dose-response relation was observed between water arsenic concentrations and skin cancer prevalence; rates were 26, 101, and 214 per 1,000 for villages with median water concentrations of 170 $\mu\text{g/liter}$, 470 $\mu\text{g/liter}$, and 800 $\mu\text{g/liter}$, respectively. In a small case-control study that followed, the prevalence odds ratios of skin cancer increased with duration of residence in endemic regions, duration of drinking well water, and water arsenic concentrations (20). The occurrence of cutaneous conditions (inferred to be skin cancers) was associated with drinking water arsenic in a comparison of two towns in Mexico, one with a mean drinking water concentration of 411 $\mu\text{g/liter}$ ("the highly exposed town") and a similar town with

TABLE 1. Selected characteristics of squamous cell carcinoma and basal cell carcinoma cases and controls, New Hampshire, 1993–1996*

Selected characteristics	Squamous cell carcinoma (n = 284)		Basal cell carcinoma (n = 587)		Controls (n = 524)	
	No.	%	No.	%	No.	%
Reference age (years)						
<40	3	1.1	42	7.2	28	5.3
40–49	17	6.0	100	17.0	66	12.6
50–59	47	16.6	123	21.0	103	19.7
60–69	116	40.9	205	34.9	206	39.3
≥70	101	35.6	117	19.9	121	23.1
Sex						
Male	182	64.1	338	57.6	315	60.1
Female	102	35.9	249	42.4	209	39.9
Race						
White	280	98.9	577	98.3	505	96.7
Non-White	3	1.1	10	1.7	17	3.3
Highest level of education						
High school or less	123	43.5	226	38.5	254	48.6
College	88	31.1	215	36.6	164	31.4
Graduate school	72	25.4	146	24.9	105	20.1
Smoking status						
Never smoked	89	31.5	251	42.8	174	33.3
Former smoker	144	50.9	248	42.3	247	47.3
Current smoker	50	17.7	88	14.9	101	19.4
Skin reaction to sun, first time in summer						
Blister	27	9.6	27	4.6	34	6.5
Peel	101	35.8	211	36.0	133	25.6
Mildly burn	128	45.4	303	51.7	263	50.6
Tan	26	9.2	45	7.7	90	17.3
Skin reaction to sun, after prolonged exposure						
Very tan	40	14.1	107	18.3	171	32.8
Moderately tan	139	49.1	276	47.1	229	43.9
Mildly tan	70	24.7	161	27.5	89	17.1
Freckle/no tan	34	12.0	42	7.2	33	6.3
Prior radiation treatment						
No	245	86.9	509	86.7	483	92.4
Yes	37	13.1	78	13.3	40	7.7
Household water supply						
Public	175	62.1	343	59.7	323	62.2
Private, drilled well	84	29.8	193	33.6	154	29.7
Private, shallow well or spring	23	8.2	39	6.8	42	8.1
	Squamous cell carcinoma (n = 284) (mean (SD)†)		Basal cell carcinoma (n = 587) (mean (SD))		Controls (n = 524) (mean (SD))	
Years used current water supply	18.1 (14.1)		15.7 (12.9)		16.7 (13.1)	

* Data were missing on race (two controls and one squamous cell carcinoma case); education (one control and one squamous cell carcinoma case); smoking status (two controls and one squamous cell carcinoma case); skin reaction to the sun, first time in summer (four controls, one basal cell carcinoma case, and two squamous cell carcinoma cases); skin reaction to sun, after prolonged exposure (two controls, one basal cell carcinoma case, and one squamous cell carcinoma case); prior radiation treatment (one control and two squamous cell carcinoma cases); household water supply (five controls, 12 basal cell carcinoma cases, and two squamous cell carcinoma cases); and mean years used current water supply (36 controls, eight basal cell carcinoma cases, and 10 squamous cell carcinoma cases).

† SD, standard deviation.

respect to “environmental and socioeconomic condition” with a mean concentration of 5 µg/liter (“the unexposed town”) (21). Similarly, drinking water arsenic contamination was linked to skin cancer mortality in a region of northern Argentina (22) with concentrations up to 960 µg/liter (23).

While these studies point to an etiologic link between drinking water arsenic and skin cancer, they do not provide data regarding the risk at lower levels of exposure. Consequently, the shape of the dose-response at these lower levels has not been determined. Several risk assessment

TABLE 2. Odds ratios and 95% confidence intervals for squamous cell carcinoma and basal cell carcinoma according to percentiles of toenail arsenic concentrations in controls, New Hampshire, 1993–1996

Toenail arsenic concentration (µg/g)	Percentile	Cases		Controls		Odds ratio*	95% confidence interval
		No.	%	No.	%		
Squamous cell carcinoma							
0.009–0.089	≤50	155	54.6	263	50.2		Reference
0.090–0.133	50.1–75	64	22.5	136	25.9	0.93	0.64, 1.34
0.134–0.211	75.1–90	33	11.6	73	13.9	0.98	0.61, 1.58
0.212–0.280	90.1–95	14	4.9	26	5.0	1.10	0.55, 2.21
0.281–0.344	95.1–97	5	1.8	11	2.1	1.00	0.33, 3.01
0.345–0.81	97.1–100	13	4.6	15	2.9	2.07	0.92, 4.66
Basal cell carcinoma							
0.009–0.089	≤50	281	47.9	263	50.2		Reference
0.090–0.133	50.1–75	156	26.6	136	25.9	1.01	0.76, 1.35
0.134–0.211	75.1–90	92	15.7	73	13.9	1.06	0.74, 1.51
0.212–0.280	90.1–95	22	3.7	26	5.0	0.72	0.40, 1.31
0.281–0.344	95.1–97	10	1.7	11	2.1	0.75	0.31, 1.81
0.345–0.81	97.1–100	26	4.4	15	2.9	1.44	0.74, 2.81

* Odds ratios adjusted for age and sex as described in the text.

models are based on linear extrapolations of the Taiwanese and Mexican data. These models suggest an excess cancer risk at concentrations below the current US maximal contaminant level of 50 µg/liter (4). In a later reanalysis of the Taiwanese skin cancer survey, a quadratic model appeared to fit the data slightly better than did the linear model, although no definitive conclusions were drawn about the shape of the dose-response curve (4). In our study, the quadratic model also appeared to fit the data. However, because of the small number of subjects at the highest and lowest levels of exposure, we had limited power to determine the exact form of the dose-response model.

An important aspect of our study is that we used toenail concentrations of arsenic as an individual biomarker of past exposure. In our population, we found that toenail concentrations were correlated with well water concentrations, particularly among those with water concentrations of arsenic of 1 µg/liter or more ($r = 0.65$) (12, 24). However, among those with lower water concentrations, the correlation was not so good, raising the possibility of misclassification among persons with low levels of arsenic in drinking water. One of the difficulties in relying on water measurements alone is that the reproducibility of water arsenic is not well characterized, and concentrations could vary seasonally or over longer periods. Moreover, estimation of exposure based on water concentrations would require careful consideration of the amount consumed and the arsenic concentrations of water sources outside the home. We chose a biologic tissue to measure exposure since, in theory, it reflects all sources of exposure. Nonetheless, it is conceivable that exposure misclassification could have attenuated our risk estimates.

The precise latency period for arsenic's effects on skin cancer remains uncertain. Therefore, our results based on toenail concentrations may not cover the relevant exposure period. Patients treated with potassium arsenite (Fowler's solution) for psoriasis and other ailments developed skin cancers from 3 to 40 years after treatment (25). In the case-

control study of bladder cancer conducted by Bates et al. (26), an elevated odds ratio of bladder cancer was observed among smokers beginning 10–19 years since exposure, with the highest risk after 30–39 years. Toenails reflect exposure in the past several months and perhaps even longer time periods. Based on data from the Nurses' Health Study (27), toenail arsenic levels were correlated over a 6-year period ($r = 0.54$). Our study population was relatively stable and remediation efforts had not occurred; over 50 percent used the same water system for over 15 years. We did not find that the relative risk estimates varied significantly by how long subjects used their water system (data not shown).

Part of the current controversy regarding the maximum contaminant level for arsenic in the United States is whether the Taiwanese data apply to the US population. Not only are the levels of exposure far lower in the United States, but the underlying risk of skin cancer in the United States is vastly greater than it is in Taiwan. BCC and SCC, together, are the most common malignancies in the United States, and the incidence rates of these malignancies appear to be rapidly increasing (14). On the other hand, the validity of our findings could be questioned since we did not obtain full cooperation from all eligible subjects. The overall age and sex distributions of non-participants were not appreciably different from those of participants; the mean age was 61 years and the proportion of men was about 40 percent in both groups (data not shown). About 20 percent of the participants and nonparticipants lived in the three major urban regions of the state (data not shown). However, we cannot exclude the possibility that arsenic concentrations differed between participants and nonparticipants. Another possible source of bias is that controls with a driver's license or Medicare enrollment may not represent the population at large. On the basis of a comparison of Medicare beneficiaries with US Census data, we expect over 90 percent coverage of residents aged 65 years and older (28). While we do not have comparable statistics for New Hampshire drivers' license records, in a study done in Iowa, drivers' license

records covered over 90 percent of the population (29). In cases interviewed for our skin cancer study, 98.5 percent of those aged 25–64 years had a valid driver's license at the time of interview, and 98 percent of those aged 65–74 were enrolled in Medicare.

In the United States and in most other countries, non-melanoma skin cancers are excluded from central cancer registries. For this reason, epidemiologic data regarding these malignancies are relatively sparse. To identify cases, we established a statewide surveillance system of dermatologists, dermatopathologists, and pathologists in New Hampshire and bordering areas. We restricted our case group to histopathologically confirmed cases. Based on a large chemoprevention trial, the pathologists' diagnostic practices are likely consistent (30). The diagnosis of nonmelanoma skin cancer in studies from Taiwan and Mexico was often based on clinical criteria that may not be reliable (31). Yeh et al. (32) performed a histopathologic review of 303 skin cancers that occurred among residents of the endemic arsenic regions. The majority were described as intraepidermal carcinomas, 19 percent as epidermal carcinomas, and 15 percent as basal cell carcinomas. All had multiple lesions. Among patients treated with Fowler's solution, squamous cell lesions were commonly associated with keratoses and basal cell carcinomas frequently occurred as multiple superficial lesions (25). In our study, we specifically excluded in situ (intraepidermal) lesions because the ascertainment of cases could be dependent on screening behavior. We were unable to analyze the risk of multiple BCCs as a subgroup because of the scant number of these cases. Thus, it is possible that both major types of nonmelanoma skin cancer relate to arsenic ingestion, but that further data are needed.

Drinking water exposure to arsenic is a global concern. Arsenic-contaminated drinking water has been detected in several regions of the world including Silesia (33), Argentina (22), Mexico (21), Chile (34), and most recently India (35) and Bangladesh (36), as well as the southwest coast of Taiwan and other parts of Asia. In the United States, it is estimated that about 350,000 residents drink water with arsenic concentrations above the current maximal contaminant level and that over 2 million consume water with arsenic concentrations above 2 µg/liter (37). Public water systems are required to have levels below the maximal contaminant level. However, private wells (serving fewer than 15 households or 25 individuals) are common in rural areas. These sources are not regulated under the US Safe Drinking Water Act. In New Hampshire, we estimate that private wells serve roughly 35–40 percent of the households and that over 10 percent of these wells have arsenic concentrations above the present maximal contaminant level (13). In summary, our findings highlight both the feasibility and need for further investigation of the potential carcinogenic drinking water levels of arsenic exposure found in the United States.

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